A 7-[2-(2-AMINOIMIDAZOL-4-YL)-ACETAMIDO]CEPHALOSPORANIC ACID

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Variations in the substituents in the cephalosporin series of antibiotics, either at the C-3 of the dihydrothiazine ring or the C-7 of the azetidinone ring, have been found to have major effects upon their antibacterial activity.1) The spectrum of this activity has been much improved recently by the introduction of the 7-[2-(2-aminothiazol-4-yl)acetamido]cephems (5).2,3) We sought to prepare a 7-[2-(2-aminoimidazol-4-yl)acetamido]cephalosporin (4) in order to compare its activity with the related 2-aminothiazole compounds. 2-Aminoimidazoles are readily prepared by the reaction of α-amino ketones with cyanamide.4) The required α-aminoketones may be prepared by a variety of hydrolytic or chemical reductive methods.5) However, most of these methods seemed inappropriate as our target aminoketone (3) contains several other chemically sensitive groups. We therefore adopted the approach of preparing an α-azidoketone, then reducing the azide catalytically to an amine. This synthetic strategy has been rarely used to our knowledge,6,5) and offers a simple method for the preparation of α-aminoketones in the presence of other sensitive functional groups.

Table 1. Antibacterial activity of 7-[2-(heterocyclyl)-acetamido]cephems (MIC: μg/ml).

<table>
<thead>
<tr>
<th>Strain</th>
<th>5</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus 663</td>
<td>0.2</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>E. coli 1850E</td>
<td>0.5</td>
<td>4</td>
<td>62</td>
</tr>
<tr>
<td>S. typhimurium 804</td>
<td>0.5</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>P. aeruginosa 850</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>P. mirabilis 431E</td>
<td>0.2</td>
<td>4</td>
<td>31</td>
</tr>
</tbody>
</table>

Treatment of the bromoester (1) with sodium azide in aqueous tetrahydrofuran gave the azido ester (2a). The ester (2a) was deprotected with trifluoroacetic acid (TFA) and the azido group of the resulting acid (2b) was reduced by hydrogenolysis over palladium on carbon, in the presence of one equivalent of TFA to prevent dihydropyrazine formation. The resulting amino ketone (3) was reacted with aqueous cyanamide at pH 4.5 to give, after purification on XAD-2 resin, the required aminomidazole (4).

The antibacterial activity of the aminimidazole (4) is poorer than that of the corresponding aminothiazole (5) (Table 1), but was notably better than that of other typical 7-[2-(heterocyclyl)acetamido]cephems (e.g. 6).

Experimental

** tert-Butyl (6R,7R) - 3 - Acetoxymethyl - 7 - (4 - bromo-3-oxobutanamido)ceph-3-em-4-carboxylate (1)**

A solution of bromine (1.02 ml, 20 mmole) in dry dichloromethane (10 ml) was added dropwise to a cooled, stirred solution of redistilled diketene (1.68 g, 20 mmole) in dichloromethane (10 ml) at -40°C. After addition was complete, the mixture was added dropwise to a stirred, ice-
cooled solution of tert-butyl 7-aminocephalosporanate (6.56 g, 20 mmole) and triethylamine (2.8 ml) in dichloromethane (100 ml). The mixture was stirred for 10 minutes, then allowed to warm to room temperature over a further 15 minutes. The reaction mixture was washed with water (3 x 100 ml), then dried (Na2SO4) and concentrated. The residue was chromatographed on silica gel (Merck kieselgel 60; 100 g), using ethyl acetate -petroleum ether (bp 40-60°C) (3: 2) eluent, to give 5.7 g (58 %) of the ester (1); IR (CHBr3) 1785, 1725, 1685 and 1520 cm-1; NMR (DMSO-d6) 5 1.50 (s, tert-butyl), 2.05 (s, -OCOCH3) , 3.44 and 3.70 (ABq, J=18Hz, 2-CH2-), 3.66 (s, -COCH2CO-), 4.42 (s, -CH2Br); resonances for H-6 (5 5.14), H-7 (6 5.76) and the amide proton (d 9.15) were split due to keto-enol tautomerization of the side chain.

Anal. Calcd. for C1gH23BrN2O7S:
C 44.0, H 4.7, N 5.7, S 6.5
Found: C 44.6, H 5.0, N 5.4, S 6.4.

(6R,7R) - 3-Acetoxymethyl- 7 - (4-azido-3-oxobutanamido)ceph-3-em-4-carboxylate (2a)
A solution of sodium azide (66 mg, 1 mmole) in water (1 ml) was added to a solution of the bromide (1) (0.50 g, 1 mmole) in THE - water (3: 1, 8 ml). After stirring for 2 hours, the mixture was partitioned between ethyl acetate and water. The organic phase was dried and concentrated to yield 0.34 g (74 %) of the ester (2a); IR (Nujol) 2100, 1786, 1728 and 1686 cm-1; NMR (CDCl3) 6 3.34 and 3.62 (2H, ABq, 2-CH2), 4.52 (2H, s, -CH2N3), 4.93 (1H, d, J=5 Hz, 6-H), 5.88 (1H, d of d, J=5 and 8 Hz, 7-H), 7.76 (1H, d, J=8 Hz, -CONH-).

(6R,7R)-3-Acetoxymethyl-7-[2-(2-aminoimidazol-4-yl)acetamido]ceph-3-em-4-carboxylic Acid (4)
A solution of the amino acid (3) (2.1 g, 4.3 m-mole), cyanamide (1.0 g, 24 mmole) and sodium bicarbonate (0.30 g) in water (25 ml) was warmed at 45°C for 2 hours. The mixture was then acidified to pH 2 with 2 N aqueous hydrochloric acid and the precipitated material filtered off. The filtrate was neutralized (pH 6) with sodium bicarbonate, then passed down a column of XAD-2 resin using water as eluent. After all cyanamide had been washed out (negative cyanamide test), the eluent was changed to water - ethanol (3: 1) and 500 ml of eluate collected. The ethanolic eluate was concentrated to ca. 10 ml. The deposited crystals were filtered off and dried over P2O5 to yield 0.25 g (15 %) of the aminoimidazole (4); IR (Nujol) 3544, 3360, 1760, 1741, 1699, 1655 and 1535 cm-1; UV (pH 6 phosphate buffer) 261 nm (s 8,700); NMR (D2O/DCI) 5 3.52 and 3.76 (2H, ABq, 2-CH2), 3.77 (2H, s, -CH2-CONH-), 5.18 (1H, d, J=5Hz, 6-H), 5.70 (1H, d, J=5Hz, 7-H), 6.72 (s, imidazole 5-H).

References